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EFFECTS OF VARIATIONS IN VOLUME PRELOAD ON LEFT VENTRICULAR FILLING CHARACTERISTICS OF OLDER NORMAL SUBJECTS.

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Left ventricular filling characteristics are known to be altered with increasing age. The effects of wide variations in volume preload on these left ventricular (LV) filling characteristics were determined by Doppler echo (DE) studies of 8 young (mean age 24 yrs) and 9 older (mean age 62 yrs) normal subjects. Preload was increased by 5 degrees of head down tilt (H) for 90 mins and decreased by lower body negative pressure (L), known to increase and decrease LV end-diastolic dimensions (EDD) by 20% in young subjects. DE recordings were made before (C) and after each change in preload; E to A peak velocity ratio (E/A PV), time velocity integrals of peak (E TVI) filling and atrial (A TVI) filling, and atrial filling fraction (AFF) were measured. (*p<0.05, C vs. H or L; §p<0.05, young vs. old).

	YOUNG			OLD		
	H	C	L	H	C	L
E/A PV	2.0	2.0	1.5*	1.3	1.1§	1.1
E TVI	13.3	13.8	9.9*	11.6	11.0	9.3
A TVI	4.4	6.3	4.2	6.6*	9.2§	8.7
AFF	25	29	30	36*	45§	46

The data show that an increase in volume preload in the older subjects increases peak filling and diminishes dependence on the atrial component of LV filling. This lack of sensitivity of the atrial filling fraction appears to be age dependent. The lack of changes in E to A peak velocity ratio tends to confirm that the age dependent changes in LV filling are related to altered stiffness rather than abnormal relaxation.

PLATELET DEPOSITION ON SEVERELY DAMAGED VESSEL WALL AT FLOW CONDITIONS TYPICAL OF STENOTIC VESSEL IS INHIBITED BY LJ-CP3. (ANTIPLATELET GLYCOPROTEIN GPIIB/IIIA MONOCLONAL ANTIBODY).

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Two of the causal factors in coronary arterial thrombosis are vascular trauma (spontaneous plaque rupture or angioplasty) and high local blood shear rate (LSR) conditions in areas of stenosis. Both factors have been shown to induce significant local platelet activation and thrombosis. Platelet activation pathways converge in the exposure of platelet GPIIb/ IIIa receptors in the platelet membrane. We have observed that the blockade of GPIIb/IIIa in dog platelets by LJ-CP3 (50μg/ml), a specific antihuman platelet GPIIb/IIIa monoclonal antibody, reduces in vitro ADP (5μM)-induced platelet aggregation (optical) by >60% and whole blood aggregation by >90% in stirring conditions. Therefore, we have studied if LJ-CP3 would inhibit platelet deposition(PD) on severely damaged vessel wall in flowing blood conditions typical of stenotic vessels. Citrated (90mM) dog blood was perfused at LSR 1690s^{-1} for five minutes in an original well characterized perfusion chamber and PD measured by ^{111}In-labelled-platelets. Hematocrit and platelet count were similar in both groups. PD on the vessel wall was inhibited by 86% with LJ-CP3 (PDx10^6/cm^2 , X ± SE: 14±4 in controls vs 2±1 in treated bloods, p<0.03). Therefore, the blockade of GPIIb/ IIIa receptors by LJ-CP3 may inhibit PD at high LSR typical of areas of stenosis when there is severe vessel wall injury.

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Poster Displayed: 9:00AM–12:00NOON
Author Present: 10:00AM–11:00AM
Hall C, New Orleans Convention Center
Thrombosis, Thromboembolism and Thrombolysis

A MONOCLONAL ANTIBODY AGAINST TISSUE FACTOR PREVENTS PLATELET-RICH ARTERIAL THROMBOSIS IN THE RABBIT

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The effects of a neutralizing monoclonal antibody (D3-ATF) directed against human tissue factor, a component of the extrinsic blood coagulation system, was studied on the prevention of platelet-rich arterial thrombus formation. Arterial thrombus was produced in the rabbit by excision, eversion (inside out) and reanastomosis of a 5-8 mm femoral arterial segment using microsurgical technique.

In this model, spontaneous platelet-rich thrombotic occlusion occurred within 20 min in all of 4 rabbits in which a non-relevant antibody (15C5E5 raised against human cross-linked fibrin, but non-reactive with rabbit fibrin) was infused intra-arterially at a dose of 12 mg/kg over 15 min, as well as in 4 rabbits in which the arterial segment, before reinsertion, was soaked in a solution of 2 mg/ml of 15C5E5 for 30 min. With D3-ATF, presoaking of the graft was associated with peristent patency in 2 of 6 rabbits (p = NS vs control antibody), whereas intra-arterial infusion at a rate of 12 mg/kg over 15 min produced persistent patency in 4 of 5 rabbits (p = 0.05 vs control antibody).

Neutralization of tissue factor on thrombogenic arterial surface can prevent thrombotic occlusion. This may have clinical relevance since tissue factor has been identified in human atherosclerotic plaque.

ANTITHROMBOTIC EFFICACY OF LOW MOLECULAR WEIGHT HEPARIN AFTER ARTERIAL INJURY IN THE PIG

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Four dosages of a low molecular weight heparin (LMWH) CY216 were compared with unfractionated heparin (UFH, [Calciparin]) and placebo in a randomized study of 51 pigs undergoing carotid arterial injury by balloon dilatation. Endpoints were ^{111}In-platelet and ^{125}I-fibrinogen deposition and macroscopic mural thrombosis (MT) in areas of deep arterial injury (a tear extending through the internal elastic lamina). Each drug was administered as a bolus (U/kg), followed immediately by an infusion of the same dosage per hour, started 15 minutes before dilatation. Animals were sacrificed acutely.

Results are mean ± SE. Thrombin times paralleled the activated partial thromboplastin time (APTT) results. LMWH (200 U/kg) produced similar anti-Xa levels to UFH but significantly less APTT prolongation, and the resultant platelet deposition and MT were considerably higher.

	Dosage (U/kg)	No.	APTT (x basal)	Anti-Xa (U/ml)	Platelets (x10^6/cm^2)	Fibrinogen (x10^{12}/cm^2)	MT (%)
Placebo		8	1.0*	0*	42±28	35±8*	63
LMWH	100	8	1.4*	1.3*	22±5	19±2*	63
LMWH	200	8	1.8*	1.7	29±12	19±4	50
LMWH	400	8	2.6	2.5*	9±12	21±3	25
LMWH	500	10	3.3	2.6*	9±2	14±4	14
UFH	100	9	3.3	2.0	11±3	12±3	14

*p<0.05 compared with UFH

LMWH is no more effective than UFH at reducing platelet deposition, fibrinogen deposition or MT after arterial dilatation. The antithrombin effect, reflected in the APTT, appears to be more important than the anti-Xa effect of heparin at preventing thrombosis.